Introduction
to a
Submolecular Biology

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1960

ACADEMIC PRESS
New York and London

I

Introduction

THE BASIC TEXTURE OF RESEARCH CONSISTS OF dreams into which the threads of reasoning, measurement, and calculation are woven.

This booklet is the reincarnation of my "Bioenergetics"[1] which was hardly more than a dream. So, it was a surprise to me to find it translated into Russian by the Academia Nauk USSR, and to find that the introduction was written by A. Terenin, a leading figure of Soviet science. Two years later, in the fall of 1959, the Atomic Energy Committee organized a meeting, in Brookhaven, on "Bioenergetics," which gave to the problem the status of a more or less well-defined field of inquiry.

Since 1957 my thoughts have assumed a somewhat more definite form and even if I am unable to present final solutions, I am capable, at least, of asking a few questions more intelligently, weaving in a few threads of measurement, reasoning, and calculation. All the same, it is not without a great deal of anxiety that I

[1] "Bioenergetics," Academic Press, New York, 1957.

publish this booklet which will be the last instance of the repetitive pattern of my being driven into fields in which I was a stranger. I started my research in histology. Unsatisfied by the information cellular morphology could give me about life, I turned to physiology. Finding physiology too complex I took up pharmacology, in which one of the partners, the drug, is of simple nature. Still finding the situation too complicated I turned to bacteriology. Finding bacteria too complex I descended to the molecular level, studying chemistry and physical chemistry. Armed with this experience I undertook the study of muscle. After twenty years' work, I was led to conclude that to understand muscle we have to descend to the electronic level, the rules of which are governed by wave mechanics. So here again, I was driven into a dimension of which I had no knowledge. In earlier phases I always hoped, when embarking on a new line, to master my subject. This is not the case with quantum mechanics. Hence my anxiety.

I have not referred to my personal history as if, in itself, it would be of any importance. I have referred to it because a most important question hinges on it: should biologists allow themselves to be steered away from this electronic dimension because of their being unfamiliar with the intricacies of quantum mechanics? At present, the number of those who master both sciences, biology and quantum mechanics, is very small. Maybe it will never be very great owing to the limited nature of human life and brain. Both sciences claim a whole mind and lifetime. So, at least for the present, developments depend on some sort of hybridization.

In my opinion, at least temporarily, the best solution does not lie in the biologists crossing over into physics, and *vice versa,* but in the collaboration of biologist and physicist. For this it is not necessary for the biologist to acquaint himself with the intricacies of wave mechanics. It is sufficient to develop a common language with the physicist, get an intuitive grasp of the basic ideas and limitations of quantum mechanics, to be able to isolate problems for the physicist and understand the meaning of his answer. Similarly, the physicist had better stay on his side of the fence rather than become, perhaps, a second-rate biologist. If, for example, as a biologist, I am interested in energy levels of a substance, and am told that the highest orbital of a substance has a k value of, say, 0.5, I can start from this point. It is sufficient for me to know what $k = 0.5$ means, and there is no need for me to know exactly how the value was arrived at. In exchange, I can bring substances to the notice of the physicist, the k value of which might be of special importance.

There is only one warning I would like to give to the biologists who venture into physical problems. There is a basic difference between physics and biology. Physics is the science of probabilities. If a process goes 999 times one way, and only once another way, the physicist will not hesitate to call the first *the* way. Biology is the science of the improbable and I think it is on principle that the body works only with reactions which are statistically improbable. If metabolism were built of a series of probable and thermodynamically spontaneous reactions, then we would burn up and the machine would run down as a watch does if deprived of its regulators. The reactions are kept in hand by being statistically improbable and made possible by specific tricks which may then be used for regulation. So, for the living organism, reactions are possible which may seem impossible, or, at least, improbable to the physicist. When Tutankhamen's grave was opened, his breakfast was found unoxidized after three thousand years. This represents the physical probability. Had His Majesty risen and consumed his meal this would have been burned in no time. This is biological probability. His Majesty, himself, must have been a very complex and highly ordered structure of nuclei and electrons with a statistical probability of next to zero. I do not mean to say that biological reactions do not obey physics. In the last instance it is physics which has to explain them, only over a detour which may seem entirely improbable on first sight. If Nature wants to do something, she will find a way to do it if there is no contradiction to basic rules of Nature. She has time to do so.*

All this makes the relationship of physicist and biologist rather touchy. The biologist depends on the judgment of the physicist, but must be rather cautious when told that this or that is improbable. Had I always accepted the physicist's verdict as the last word, I would have given up this line of research. I am glad I did not. One can know a good theory from a bad one by the former's leading to new vistas and exciting experiments, while the latter mostly gives birth only to new theories made in order to save their parents.

* Living Nature also often works with more complex systems than the physicist uses for testing his theories.

Since I am working on my present line everything seems more colorful and I am even more eager to get to my laboratory in the morning than ever before.

The biologist, embarking on this line, is neither without help nor without encouraging examples. C. A. Coulson, in the first volume of the "Advances in Cancer Research" (Academic Press, New York, 1953) has written an admirably clear unmathematical review of the basic concepts of quantum mechanics. In the third volume of the same reviews (1955) A. and B. Pullman wrote equally clearly about complex indices. Those who like to read French may find a more comprehensive review by the same authors in "Cancérisation par les substances chimiques et structure moléculaire" (Masson, Paris, 1955). For details and some mathematics one may apply to B. and A. Pullman's "Les théories électroniques de la chimie organique" (Masson, Paris, 1952). The other extreme, a very brief and popular summary, is found in B. Pullman's "La structure moléculaire" (Presses Universitaires France, 1957). Naturally, L. Pauling's "The Nature of the Chemical Bonds" (Cornell University Press, 1948) should not be missing from one's desk, nor Th. Förster's "Fluoreszenz Organischer Verbindungen" (Göttingen 1951). Its next (English) edition is eagerly awaited.*

As encouraging examples of the fruitfulness of this field I would like to mention the bold pioneering stud-

* In spite of these splendid contributions it is difficult to deny that an up-to-date comprehensive treatment, written especially for the biologist, in a possibly unmathematical language, is badly needed.

ies of A. and B. Pullman which started with the study of the electronic structure of carcinogenic hydrocarbons, in which correlations of electronic structure and carcinogenic power were established, which may be one of the first major steps toward understanding cancer. If this booklet does not contain a chapter on this subject this is because the Pullmans have, themselves, given an account of their work which could not be equaled in clarity. The same authors have broken ground also in various other fields of quantum mechanical biology, establishing electronic indices for many biologically important catalysts,[2–4] and venturing even into the field of enzymes[5] and high-energy phosphate bonds.[6]

While the quoted examples may encourage physicists interested in biology, B. Commoner[7–10] and his associates may be quoted for their pioneering studies in electron spin resonance to cheer biologists interested in submolecular phenomena. It was this work

[2] B. Pullman and A. Pullman, *Proc. Natl. Acad. Sci. U.S.* **44,** 1197, 1958.

[3] B. Pullman and A. Pullman, *Proc. Natl. Acad. Sci. U.S.* **45,** 136, 1959.

[4] B. Pullman and A. M. Perault, *Proc. Natl. Acad. Sci. U.S.* **45,** 1476, 1959.

[5] A. Pullman and B. Pullman, *Proc. Natl. Acad. Sci. U.S.* **45,** 1572, 1959.

[6] B. Pullman, *Radiation Research,* 1960.

[7] B. Commoner, J. Townsend, and G. E. Pake, *Nature* **174,** 689, 1954.

[8] B. Commoner, J. J. Heise, B. B. Lippincott, R. E. Norberg, J. V. Passoneau, and J. Townsend, *Science* **126,** 3263, 1957.

[9] B. Commoner, B. B. Lippincott, and Janet V. Passoneau, *Proc. Natl. Acad. Sci. U.S.* **44,** 1099, 1958.

[10] B. Commoner and B. B. Lippincott, *Proc. Natl. Acad. Sci. U.S* **44,** 1110, 1958.

which led to the first direct experimental evidence for the participation of free radicals in the one-electron enzymic electron transfer, as outlined in the classic studies of L. Michaelis.[11]

[11] L. Michaelis, Fundamentals of Oxidation and Reduction, *In* "Currents in Biochemical Research." D. E. Green (Ed.), Interscience Publ., New York, 1946.

II

Why Submolecular Biology? The Problem is Stated

LOOKED AT FROM A DISTANCE, THE HISTORY OF biochemistry seems to be but a series of astounding successes, a blaze of glory. The rate of progress shows no decrement and it looks as if soon we could strike out "don't know" from our vocabulary, altogether. Why, then, talk about "submolecular biology" until molecular biochemistry has run its full course?

There is no doubt about these successes. All the same, if one does not allow oneself to be blinded by them and approaches biochemistry with a dark-adapted eye, big gaps in our knowledge become evident. Let us consider some of the main problems of chemical biology, starting with metabolism. Biochemistry has unraveled the complex cycles of intermediary metabolism and has shown that the main object of this metabolism is to prepare the foodstuffs for their final oxidation in which their energy is used to couple one molecule of phosphate to ADP, producing, thereby, ATP (Fig. 19). In this process the energy of the foodstuff is translated into the energy of the terminal "high-energy phosphate bond," ~, of a very specific molecule. It is only in this form that the energy of the foodstuffs can serve as fuel for the living machinery and drive it. This "oxidative phosphorylation" is thus the central event of metabolism. Its mechanism is completely unknown.

We are equally ignorant about the reversal of this process, the release of the energy of the $\sim$ of ATP. How these $\sim$'s drive life, how their energy is translated into various forms of work, *w*, be they mechanical, electrical, or osmotic, we do not know, although this transformation may be the most central problem of biology. We know life only by its symptoms and what we call "life" is, to a great extent, but the orderly interplay of these various *w*'s; since the dawn of mankind, death has been diagnosed, mostly, by the absence of one of these *w*'s, expressing itself in motion. We do not know how motion is generated, how chemical energy is transformed into mechanical work.

Physiology has shown that the various functions of our body are regulated and coordinated by hormones and the biochemist will proudly show the row of vials containing these mysterious hormones mostly in the form of nice, crystalline powders, some of which might have been prepared synthetically. The same is true for the various vitamins, the catalogue of which seems near completion. The biochemist will be able to give us the structural formula of most of these substances. The really intriguing problem, however, is not what these substances *are*, but what they *do*, how they act on the molecular level, how they produce their actions. There is no answer to this question. The same holds true also for the majority of drugs.

As to the living machinery itself, the biochemist will tell you that its central parts are proteins, nucleic acids, and nucleoproteins. He will point out the great progress made in the structural analysis of these substances, show their building blocks, amino acids and nucleotides, their links and relative position, will speak about bond angles and distances and the various helices formed. But, if we ask why Nature has put together that very great number of atoms in that very specific way, what property did she want to achieve, our biochemist will become silent. One of the basic principles of life is "organization" by which we mean that if two things are put together something new is born, the qualities of which are not additive and cannot be expressed in terms of the qualities of the constituents. This is true for the whole gamut of organization, for putting electrons and nuclei together to form atoms, atoms to molecules, amino acids to peptides, peptides to proteins, proteins and nucleic acid to nucleoproteins, etc. What Nature had in mind when doing this we cannot even guess at present. So here, too, we find the door to the central problem locked.

There are various circumstances which make this situation rather disturbing. First, these unanswered questions are the central and most intriguing problems of biology. Another rather disturbing fact is that corresponding to lacunas in our basic knowledge, there are lacunas in medical science and a great number of "endogenous" or "degenerative" diseases still rampage freely, causing endless suffering. But the most disturbing fact is that while biochemistry is still progressing in the fields where it has already been successful, it makes practically no progress in solving the problems mentioned. It looks as if the problems of biology could be divided into two classes: those which current biochemistry can solve and those which it cannot. It looks as if something very important, a whole dimension, might be missing from our present thinking without which these problems cannot be approached.

There is no doubt in the author's mind what this missing dimension is. The story is simple and logical. Biochemistry came into bloom at the end of the last century. At that time, matter was thought to be built of very small, indivisible units, atoms. Molecules were the aggregates of these atoms. There were about 90 different sorts of atoms which were symbolized by various letters, while their links were denoted by dashes. No doubt, this letter-and-dash language ranks among the greatest achievements of the human mind and is responsible for all the amazing successes of biochemistry. If we go through the list of problems enumerated above, we will find that the ones with which biochemistry was successful were problems of structure, or changes of structure taking place in simpler reactions which could be duplicated mostly in homogeneous solutions, and could be expressed and answered in terms of letters and dashes, while the problems which remained unanswered were problems of function of complex systems which cannot be expressed in this language. How could a reaction such as muscle contraction, the main product of which is not a substance, but work, w, be expressed in these terms?

The language of current biochemistry is still that of letters and dashes which means that this science is still moving in the same molecular dimension as it was moving at its birth in the last century. But since that time its parent science, chemistry, allying itself with physics and mathematics, made a dive into a new dimension, that of the submolecular or subatomic dimension of electrons, a dimension the happenings of which can no longer be described in the terms of classic chemistry, the rules of which are dominated by quantum, or wave, mechanics. Looked at through the glasses of this new science the atom is no more an indivisible unit but consists of a nucleus surrounded by a cloud of electrons with varying and fantastic shapes, and it seems likely that the subtler phenomena of life consist of the changing shapes and distributions of these clouds.

Biochemistry did not follow its parent science, chemistry, into this new subatomic dimension, which may hold the key to the understanding of the subtle biological functions. An example may illustrate the point. On the left side of Fig. 1 stands the classic

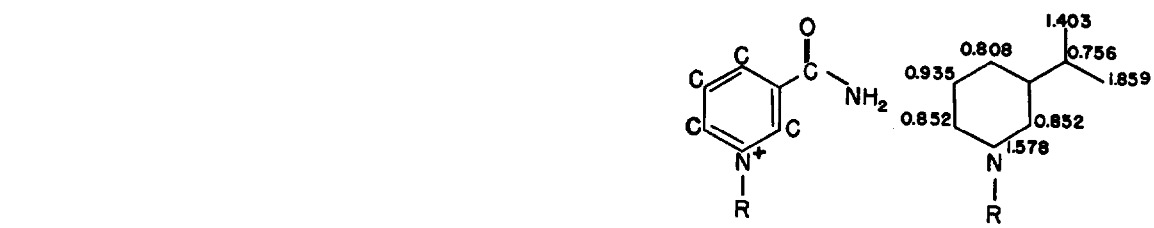

FIG. 1. Classic formula and molecular diagram of the pyridine end of DPN.

formula of the pyridine end of DPN expressed in classic symbols. It tells us that the pyridine ring is built of five equal C atoms and an N which has a positive charge. On the right side of the same figure is the "molecular diagram" of the same substance, as found in a recent publication of the Pullmans.* The numbers coordinated to each atom indicate the electric charge. They tell us that each atom has a different charge and the molecule is thus surrounded by an electronic cloud of very complex structure. The positive charge is divided unequally over the one N and five C atoms of the ring while the negative charges are relegated to the side chain. This figure should be completed by three more sets of numbers, one set giving information about what is called the "free valency" of the single atoms of the ring, the other describing the "bond-order" of the links, and the third giving the "localization energies." While the classic formula attributed to the whole molecule but an overall shape and a dipole moment, in the molecular diagram every atom of the ring assumes a personality, a profile, a high degree of specificity and the whole structure begins to assume that subtlety which we can expect from any structure taking part in biological reactions.

While atoms and molecules were revealed to be complex little universes, their strict individuality has been broken down by "solid state physics." If many atoms form a regular and closely packed system, they may develop new properties. If, for instance, a great number of copper or iron atoms get together in a specific order they may develop electric conductivity, which is a collective property due to the interaction of the wave mechanical properties of the single units. Even macromolecules may develop solid state properties. So, in order to approach the central problems of biology we have to extend our thinking in two opposite directions, into both the sub- and supramolecu-

* Ref. 3, page 6.

lar. The two, in a way, are identical, the supramolecular qualities being but the collective action of the submolecular factors, supplying a new example of "organization." Similarly, we can expect entirely new properties to develop also when these molecules or molecular aggregates interact with the general matrix of life, water, forming with it a new and unique system. The elucidation of all these interrelations may eventually lend to our thinking the plasticity which may be necessary to approach life and the meaning of that unique system called the "cell."

The approach to these new dimensions may be a difficult one, and many of the ideas to be presented here may seem hazy and doubtful. The unknown offers an insecure foothold. What admits no doubt in my mind is that the Creator must have known a great deal of wave mechanics and solid state physics, and must have applied them. Certainly, He did not limit himself to the molecular level when shaping life just to make it simpler for the biochemist.